pointed to us, with a large standard deviation indicating a large biological variability of this measure.

This slide gives all the available data, including the comparators for QT change. If you look at Telithromycin for study -- all subjects in all studies, or controlled studies all the different comparators, please note the change in QT interval is small and with the large standard deviation. In addition, we have also provided QT dispersion which is the difference between the short and the longest interval which are very similar between the different comparators.

Remember we had over 150 patients in whom we collected a PK sample with the electrocardiogram and these were done within one hour of each other. If we look at the change in plasma concentration versus the change in QTc interval, we notice a shallow slope relating the plasma concentration to the QT interval change of about 0.8 milliseconds per microgram per milliliter of the drug. Notice that there is a large capture in values particularly at low concentrations and even the patient who had the highest concentration fell on the line of regression. Since, as Dr. Ruskin pointed out, we need to know what the outliers are, I

would like to now show you who these highest 15 subjects are about one percent of the population.

Here are the concentration range for these subjects spanning from 5.2 to 9.9 micrograms per milliliter. Here are the absolute increase in QT, up to a maximum of [illegible] and here are the delta QTc's spanning from minus 38.8 in a patient with 6.4 micrograms per liter, up to 18 increase in a person with 6.7. Of note, the patient with the highest plasma concentration had only an increase of 8.7 milliseconds consistent with our slope. Clearly we need to know more about the outliers because as we heard from the post-marketing surveillance data, it had a significant number of values are the highest values that are important in addition to what we also heard from Dr. Ruskin about the occurrence of large number of patients with values higher than 500 milliseconds in the studies he quoted to us.

Here we look at the examination of the QTc change by greater than 30 or less than 60 milliseconds or greater than 60 milliseconds, or where there was an absolute increase greater than 454 men or 474 women or greater than 500 for both. Notice in comparison to Clarithromycin, the numbers are the same. I would like to note for you that none of our subjects had an

increase greater than 60 milliseconds and an absolute increase greater than 450 or 470.

We will now compare clarithromycin to non-macrolide comparators. Again, the numbers are broken down the same way and there is a small increase in the number compared to the non-macrolide comparators but very importantly, there are again nobody greater than 60 milliseconds and greater than 450 or 470 absolute increase. Probably more interesting and important are the effect of the drug in special populations, particularly elderly, particularly those with hepatic impairment, renal impairment, et cetera.

This and the other slide gives the difference subsets that we examined as the number of patients in these categories. Notice that some of the categories had small number of subjects whereas the others had fairly large number to give some meaningful information. Again, I would like to point out to you the absolute changes are small and again, the larger biological variability as shown by the standard deviation. Whether we look at age, hepatic impairment, renal impairment or taking of the concomitant CYP3A inhibitors, we did not see a major change in the QTc.

We will now also examine other variables

such as those receiving QT prolonging drugs, hypokalemia, we had 103 subjects with hypokalemia and/or diuretic therapy, those who had cardiovascular disease including hypertension and/or left ventricle hypotrophy congestive heart failure, et cetera, and also those who had prolonged or acquired QTc at baseline. Again, we see a small change in the setting of a large standard deviation.

Of note, patients with acquired QT prolongation had an 80 millisecond decrease on treatment the details of which are given on this slide which looks at all the changes in our study population. Of particular note, patients who had prolonged QT at baseline tended to show a decrease whereas those who had the shortest QT interval tended to show an increase. This is of some importance because often patients who have got acquired QT prolongation could have underlying cardiac disease or cardiovascular respecters and could unexpectedly respond by further prolongation of the QT interval.

Now let me also share with you the occurrence of treatment related adverse events that could be potentially be related to QT interval prolongation. We looked at the various categories and other than for the dizziness the occurrence of other

symptoms are very similar. There was a slight excess occurrence of dizziness but most of these cases were mild and were not associated with any change in the QT interval when compared to the comparators.

I would also like to recall for the panel the remark made by Dr. Ruskin that often it's very difficult to interpret the finding of dizziness. Let me now turn to the Phase I program. Recall from your briefing document in our Phase III program where patients received Telithromycin, there was a decrease in heart rate. However, when we went ahead to do studies in our Phase I program involving normal volunteers who often have resting low heart rates, in the 50's or even 60's or 65's, often sinus bradycardia, we saw a significant increase in heart rate with Telithromycin. So in examination the different doses up to 3.2 grams of Telithromycin which is four times therapeutic dose, we also wanted to examine the robustness of correction by the QTc formula as indicated by Dr. Ruskin and to see whether alternate formulas would be required to better interpret the changes in QT interval.

This gives us the available information with respect to the different correction formulas. Here is the change in the QT interval and after

correction of the QT interval by Bazett's formula, if you'll look at the relationship to change in heart rate, there is still a strong residual correlation. And an expedient formula mentioned by Dr. Ruskin Fredericia removes that relationship better but there is still a residual correlation.

Therefore, as it has been done by some of the FDA divisions, we also examined what would be a better formula or exponent to correct this relationship and using our baseline drug free data, we developed an exponent of 0.284 which removes the dependency completely. So for my rest of my presentation I will show you the data as QTm but keep in mind the QTc data and the QTf data are also provided in your briefing document.

If you look at all the available Phase I program, spanning from 800 to 3.2 grams of drug intake, there is a range of plasma concentration up to 7.6 or 7.7 micrograms per milliliter. Again, we observe a shallow concentration relationship to QT change of about 1.01 millisecond. If you were to look at this data by QTc, you would see a slope of about 3.9, showing the effect of heart rate and the better correction by this formula away from the heart rate dependency. Very importantly I would like to next

share with you three special drug interaction studies that we performed that is very important to evaluate the safety of Telithromycin; interaction with Ketoconazole, interaction with Cisapride and interaction with Sotalol.

This slide summarized our finding in the Ketoconazole interaction study. Both with placebo and Telithromycin there was a 3 millisecond prolongation in the QTn when the drug was administered to the patients. Again, notice the large standard deviation in these subjects. When Ketoconazole was administered, there was a 10 millisecond prolongation. When Ketoconazole and Telithromycin were given together, although there was about a 1.54 increase in Telithromycin concentration, there was little or no change in the QT measured in this study. I would like you to place this in perspective. For example, with Terfenadine, when administered with Ketoconazole there is a 16 to 72-fold increase in plasma levels and a 60 to 80 millisecond prolongation in the QT interval.

This slide illustrates the finding from out Cisapride/Telithromycin interaction study. Please recall the study was designed to examine the effect of Telithromycin on an increasing Cisapride blood level and its effect on QT. It was not designed as a head

to head comparison between Telithromycin and Cisapride. During the placebo period or during the Telithromycin period or during the Cisapride period there is a small change in the QTn of about 1 to 3 millisecond and they were not significantly different from each other throughout most of this period.

But when Telithromycin is given with Cisapride, there's approximately a doubling of the Cisapride plasma level and at peak there is a 10-millisecond prolongation in the QT interval. Again, I would like to place this in perspective by recalling for you that when you administer Cisapride with Ketoconazole, there is at least an eight-fold increase in plasma level and about a 60 millisecond prolongation in the QT interval.

Next I would like to present to you our finding from the Sotalol/Telithromycin interaction study. The first row gives the Sotalol plasma concentration achieved during the placebo period when Sotalol alone was given or in the presence of Telithromycin. Telithromycin produced a decrease in Sotalol level. If you look at the QTn or the change in QTn, there was 76 millisecond observed with Sotalol whereas in the presence of Telithromycin, it was 58 milliseconds. Since there was a change in the plasma

concentration, we also examined the slope to put this in perspective and if you'll look at the different slopes it was 45 versus 48 not different from each other. So we feel that in the presence of a type 3 mix with Sotalol, Telithromycin does not increase the risk for changes in QT interval.

Next I would like to share with you a special study in special population that was conducted with the -- at the recommendation or suggestion of the FDA to characterize the safety of Telithromycin in patients with cardiovascular risk factors. To our knowledge this is the first such program in an anti-infective area. This involved 24 subjects with congestive heart failure, ischemic heart disease, either vascularized or non-vascularized, non-life threatening arrhythmias or valvular heart disease, et cetera, who were exposed to either Telithromycin 800 milligram or 1600 milligram to either therapeutic dose or Clarithromycin, 500 milligram twice a day or placebo with all subjects receiving all four periods in our cross-over design.

These patients had electrocardiogram and 24-hour Holter monitoring before and after treatment. Here are the changes in plasma Telithromycin concentration on 800 and 1600 milligram and

Clarithromycin for comparison. Here are the change in QTn which was not different between Telithromycin 800 or 1600 and here is the Clarithromycin data for comparison. If you look at QTc because the drug had, again, a large effect on heart rate, the changes in QTc are a little bit more prominent but again, in the context of the variability, they remain small.

Of note, there was no evidence of arrhythmias on the Holter monitor in any of these subjects. This slide gives all the plasma concentration data in these 24 subjects in the two different periods for 800 and 1600 milligram of Telithromycin. Again, we note a shallow relationship between QTn or change in QTn and the plasma Telithromycin concentration. Again, if this were to be using QTc, the slope will be higher because of the effect on heart rate. To put these findings in perspective, I would also like to share with you the data from Phase III program where we had more than 280 subjects with underlying cardiovascular disease.

Again, here is the change or the measured plasma Telithromycin concentration and the change in QTc and we notice little or no slope in patients who are -- who will actually receive the drug in clinical practice.

In conclusion, Telithromycin had a wear effect in Ikr channel and importantly in patients with respiratory tract infection who will receive the drug, we observed a small change in QTc of about approximately one millisecond. There was a shallow relationship between QTc and plasma Telithromycin concentration over a wide range. There was no difference in the occurrence or frequency of outliers of QTc between Telithromycin and macrolide or non-macrolide comparators.

Analysis of different at risk populations did not reveal a propensity for enhanced effect on cardiac repolarization. Very importantly, we did not notice any cardiovascular adverse events such as Torsades, admittedly cannot be detected in such a small population but also absence of ventricular tachyarrhythmias, absence of syncope or -- that could be associated with QT prolongation.

As sponsor, we believe that we have defined the risks associated with the change in plasma Telithromycin concentration. The strong Phase III data, the shallow relationship between plasma Telithromycin concentration and change in QTc, the high viability of the drug, the availability of multiple mechanism for this compound including a heart

rate that cannot be blocked by clinically available drugs and the compensatory increase in renal excretion in patients with hepatic impairment strongly limits the possibility that there could be an unexpected increase or large increase in plasma concentration of Telithromycin in clinical use and potential for acute cardiac repolarization changes.

I would now like to ask Mindell Seidlin to come and conclude the presentation.

CONCLUSIONS OF DR. MINDELL SEIDLIN

DR. SEIDLIN: As illustrated earlier, there is a clear need for new oral antibiotics for treatment of respiratory tract infections. The prevalence of high level resistance to both Penicillin G and Erythromycin A in the United States exceeds 15 percent now. Resistance to other agents including Cotrimoxazole, Tetracyclines and others have increased as well. Resistance to Quinolones has been reported. The term multi-resistance has now been applied to the pneumococcus. There is increasing evidence that resistant strains of pneumococci are associated with clinical failures and adverse outcomes.

At the same time, it is important that respiratory antibiotics provide effective therapy for the full range of pathogens involved in these

infections. The current medical environment is one with increasing numbers of elderly patients and patients with numerous underlying illnesses taking a variety of concomitant medications. In the past, many of these patients might have been hospitalized for treatment of community acquired pneumonia or acute exacerbation of chronic bronchitis. More and more these patients are being treated in the community.

The initial choice of effective oral therapy in these patients is crucial. Telithromycin is the first in a new class of antibiotics, the Ketolides. It has a novel mode of action which two binding sites to the 23 SR&A of the 50S ribosomal subunit. This accounts for its superior activity against sensitive strains of the pneumococcus and retained activity against Erythromycin A and Penicillin G resistant strains. It is also active against the other key respiratory pathogens, common, atypical and intra-cellular.

Telithromycin has a well-characterized and reproducible pharmacokinetic profile. Therapeutic levels are rapidly achieved in plasma, in infected tissue and inside cells. Telithromycin was consistently effective in all analyses in 13 clinical trials in the four proposed indications. Of special

note in the studies of community acquired pneumonia, cure rates in the elderly were 90 percent. Likewise they exceeded 90 percent in patients with pneumococcal bacteremia. Cure rates were high in patients with atypical infections and all cases of Legionella were cured.

In the other three indications, the five-day once daily regiment was demonstrated to be as effective as 10-day coursed of comparator regimens despite stringent criteria which could have favored longer duration therapeutic regimens. Efficacy was also demonstrated in community acquired pneumonia and in sinusitis in patients with infections due to Penicillin and Erythromycin resistant pneumococci.

Safety was evaluated in 3,265 patients which included a broad array of ages, underlying illnesses and concomitant therapies. Gastrointestinal adverse events were the most common identified and occurred in a range that is well-recognized in oral antibiotic therapy. Hepatic events and transaminase elevations were uncommon and occurred at rates comparable to those of comparative ages.

Discontinuation of therapy and serious adverse events were rare and occurred at rates similar to the comparators. A thorough evaluation of the

effect of Telithromycin on cardiac repolarization revealed a weak effect on the Ikr channel and approximately one millisecond increase in the QTc interval in patients with respiratory infections. No cardiac adverse events attributable to this change were observed.

The effect is similar in magnitude to that of widely used antibiotics. We anticipate that our planned post-marketing surveillance program will confirm the safety profile observed in the Phase III trials. I will conclude by summarizing the benefits that Telithromycin will bring to patients.

It is highly effective against the pneumococcus, the pathogen most associated with morbidity and mortality in respiratory infections. It is active both in vitro and in patients with Penicillin and Erythromycin resistant strains of *S. pneumoniae*. It is a single agent which is effective against all of the key respiratory pathogens, common, atypical and intracellular. The brief five-day regimen in common infections is likely to enhance patient compliance.

Currently there are few therapeutic options for out-patients with respiratory tract infections who are at risk for drug resistant *S.*

pneumoniae. Telithromycin will effectively and safely expand those options. Thank you.

DR. RELLER: Thank you, Dr. Seidlin and your colleagues for the Aventis presentation. These presentations are now open for discussion and questions directed to the presenters. Dr. Bell?

DR. BELL: The safety presentations were appropriately most focused on the cardiac issues and I guess we're going to hear more about that from the FDA this afternoon but I wonder if one of you would be kind enough to elaborate on the blurred vision issue. I seem to recall that in the tonsillitis studies there were maybe half a dozen people and I think maybe mostly woman who were who had blurred vision versus none in the comparator group and one of the speakers referred to this as transient myopia.

And I guess I'm -- could you please talk a little bit more about that? For example, how transient was it and how do you know that this wasn't a potential harbinger of some more serious neurologic or opthamologic event that just didn't complete? Can you just talk a little more about that?

DR. SEIDLIN: I'd be happy to. You pointed out correctly that most of the cases of blurred vision did occur, in fact, in young women in

the tonsillitis/pharyngitis trial. Most of them lasted for a matter of a couple of hours and resolved while the patients were still on therapy. We actually observed blurred vision at high doses in some of the Phase I trials and had the opportunity to conduct opthamologic exams in those patients. In those patients, there were no abnormalities observed in the fundi and in the lens and the retina, et cetera, and the opthamologist concluded that there was a difficulty in accommodation accounting for the blurred vision.

We believe that the mechanism related to this probably has to do with a cholinergic effect of the drug which is generally a mild effect but maybe having more impact on the eye muscle.

DR. RELLER: Dr. Murray?

DR. MURRAY: In the examination in animals of retina or optic pathways, anything pathologically done?

DR. SEIDLIN: There were pathologic examinations of the eye. I'm going to call upon Dr. Miller to detail those for you.

DR. MILLER: We did carry out extensive examinations within the pre-clinical program. This included a peer review of the retinas from the repeat

dose toxicity studies in the rats, the dogs and the monkeys and within the monkey one month toxicity study we also measured and recorded electra-retinograms and we saw no adverse effects in any of these examinations.

DR. RELLER: Dr. Lazzara?

DR. LAZZARA: Just in the Sotalol experiments, the Sotalol trials, I'm sorry, for which Sotalol was combined with Telithromycin, the -- you didn't give the dose of Sotalol that was given, 160 BID. And I was -- the delta QTn, that's your QTn correction, that was the QTn on Sotalol versus the QTn at baseline?

DR. SEIDLIN: I'm going to ask Dr. Benedict to come to the microphone so that he can better respond.

DR. BENEDICT: Yes, the QTn product was developed on QTn for Sotalol.

DR. LAZZARA: So it was a mean 76 milli-second prolongation on Sotalol.

DR. BENEDICT: Right, on Sotalol, yes.

DR. LAZZARA: The other point about the Sotalol experiments, was the -- the heart rates would have been then, I guess, fairly low. Do you have any data on what the heart rates were on the Sotalol when

the Telithromycin was added?

DR. BENEDICT: I think we did not see any additional change in -- no, there was additional change on top of Sotalol of about four to five beats.

DR. LAZZARA: Decrease?

DR. BENEDICT: Increase in heart --

DR. LAZZARA: Increase with the Telithromycin.

DR. BENEDICT: Right.

DR. LAZZARA: Thank you.

DR. KELLER: Yes, Dr. Moss?

DR. MOSS: Could we get some detail on just how the QT interval was measured, because at least in one of the slides it appeared that one took the longest QT minus the shortest QT or not minus, but averaged the time, the QT interval between the longest and shortest and used this as -- and then corrected for it; is that correct?

DR. SEIDLIN: Yes, that's correct.

DR. MOSS: Do you have any data on simply what was the longest QT, not averaging between the longest and shortest?

DR. SEIDLIN: Dr. Benedict?

DR. BENEDICT: Yes, we have that data available but we provided the QT dispersion and since

we did both the averaging for the pre and on treatment, we felt the change would be the same because it's being averaged, but on the whole, to answer your question what was the longest, the longest would have been about 10 milli-seconds more than what would have reported for the absolute QT but in terms of the delta QTc, it would have been no different.

DR. MOSS: That delta QTc would have been no different using the -- your end correction, your exponent that's different from the Bazett or Fridericia?

DR. BENEDICT: For the Phase III program, we presented the Bazett formula QTc correction. So at least in that population, we saw the changes were approximately similar, the same or similar whether we did the averaging or we took the longest.

DR. MOSS: And did you do any corrections for the placebo, that is there is some prior data that I've seen for the various doses, the 800 and 1600 milligram doses, on the QTc Bazett and after -- with subtraction of the placebo and adjusted for the placebo and it was really quite considerable the QTc changes.

DR. BENEDICT: Yes, because the doses ranging from 800 to 3200 milligram were studied in

normal, healthy volunteers often with heart rates as low as 60, even some having rates lower than 60 and in this individual there was an increase in heart rate so if we just use the QTc formula we see a slope of about three to four milli-seconds per microgram per milli-liter of the drug but when we appropriately now correct for the effect of the heart rate using QTn formula, the slope is now about 1 milli-second per micro-liter per milli-gram of the drug.

DR. MOSS: Could you give some idea of what the average heart rate changes were?

DR. BENEDICT: Yes, the average heart rate change, I think we have a slide on that. Okay, while the slide is coming up, the average heart rate in the normal volunteers I would say was about approximately in the region of about five to eight beats per minute.

DR. MOSS: Right, and let me just ask one final question. I notice there were 95 subjects in the age range of 13 to 18 years. Two questions, were they given the same dosage or was the dosage attenuated for body weight and have you studied any children younger than age 13?

DR. SEIDLIN: The 13 to 18-year olds were all treated with 800 milligrams once a day, so the dose was not adjusted in those teenagers. We are

currently carrying out a pediatric program but that data has not yet been submitted to the agency.

DR. RELLER: Dr. Sumaya, did you have a question?

DR. SUMAYA: Yes, it's somewhat related to the latter question. Do the sponsors feel that the potential utilization of this drug amongst various age groups correlates with the amount of studies done in those age groups in both efficacy and in safety? In other words, the ones that are going to use this more have been the ones most studied? Is there some rough comparability?

DR. SEIDLIN: Well, we did cover the age range of patients anticipated to take this drug in marketed use. Whether they are in direct proportion is always hard to say, but we certainly did cover the adolescents, the vast majority of patients between 18 and 65 and a substantial number of patients over 65.

DR. RELLER: Yes, Dr. Lee.

DR. LEE: Yes. Could somebody address the paddock metabolism that's non-P450? Is that glucuronidation, is it -- do we know?

DR. SEIDLIN: Dr. Bhargava?

DR. BHARGAVA: The metabolism of Telithromycin is by several metabolites and one of the

major metabolites that's the circulating species is the RU-363 which is loss of the areal grain. And that is the pathway that is metabolized by the non-cytochrome P450.

DR. RELLER: Yes, Dr. Moss.

DR. MOSS: I'm struck by the enormous standard deviations of the measurements. Do you want to provide any explanation that is with mean value of delta QTc of [illegible] milli-second and a standard deviation of 21 milli-seconds? I know you touched on this as outliers but that just seems like an enormous variability.

DR. SEIDLIN: We believe that this is attributable to the biologic variability of this parameter and the errors in measurement which are common. There is also a great deal of spontaneous intra-individual variability, it's hard to say but it exists anyway, which is accounted for by this.

DR. MOSS: Was the QT measurement done by manual or was it machine read with operator over-read or what?

DR. SEIDLIN: There was operator over-read for all EKG's.

DR. MOSS: No, but the primary measurement was machine read?

DR. SEIDLIN: I'm going to ask Dr. Benedict to talk about the parameters for reading the ECG's.

DR. BENEDICT: When the electrogram was originally performed at the site, there was a machine over-read for safety evaluation on the spot for the investigator. But then all the electrocardiograms were transmitted to a central reader who blindly manually read every single electrocardiogram looking at all the 12 leads.

DR. RUSKIN: Can you describe the methodology by which they were read? Was this on a standard ECG? Were they computer read at high speed or how was it done?

DR. BENEDICT: These were all standard 12 lead electrocardiograms at 25 millimeter per second paper speed and using the standard criteria for measuring the QRs interval.

DR. RELLER: Yes, Dr. Lazzara.

DR. LAZZARA: Another question about the hypokalemia trial, can you give us an idea of the severity of the hypokalemia?

DR. BENEDICT: Yeah, we did not specifically do a study on patient population of hypokalemia. We included all patients who had

potassium less than 3.5 milli equivalents per liter and we had approximately either about 60 to 70 patients with potassium less than 3.5 or 40 to 50 patients who are receiving concomitant diuretic therapy and that's where we have the data from that group.

DR. LAZZIO: Yeah, but I was curious as to do you have a mean, say what the potassiums were in that groups?

DR. BENEDICT: I don't have it right now. I think we can provide it to you later on.

DR. RELLER: Dr. Davis.

DR. DAVIS: Can you say some more about these Japanese studies? They were included and then excluded in this count for the question of resistance.

DR. SEIDLIN: Uh-huh. We only presented the resistance isolates from the Japanese studies. We did not present the overall safety or efficacy from those studies. The study design in Japan was a little bit different from the study design in the U.S. In Japan, the -- there was seven days of therapy whereas in the U.S. there was seven to 10 days depending on which study.

The end of therapy visit in Japan was at seven days and then there was a follow-up visit at

post-therapy which was corresponded to our 17 to 21-day visit and that was used as the end point for those studies. The severity criteria for enrollment in the Japanese study were slightly different and none of those patients had blood cultures which is why we had no bacteremias. It may have been why we had no bacteremias in those studies. However, the cultures were all done and the MICs determined by NCCLS criteria and the clinical criteria for cure were quite similar.

DR. DAVIS: You said the severity was different. So the severity was less.

DR. SEIDLIN: Not necessarily less. They actually used a different severity measure in those studies. So they were graded in a slightly different way.

DR. RELLER: The last two questions to Dr. Seidlin were posed by Dr. Barry Davis. Dr. Chesney?

DR. CHESNEY: I had a question about emergence of resistance and I wondered if isolates -- you made any attempt to look at isolates that might have still been present on therapy and after therapy and did you detect any emergence of resistance and then in the briefing document there is the comment, "While exposure to Telithromycin did select for

pneumococcal mutants within increased MICs, most remained within the proposed susceptibility range", and I wondered if you could just elaborate on that a little bit for us.

DR. SEIDLIN: To the first part of the question we did not identify any Telithromycin resistant mutants in patients who had been treated in the program. The comment refers to attempt to select resistant mutants in the laboratory by serial passage and we'd be happy to present that data. Dr. Bryskier?

DR. BRYSKIER: So we did -- one study was performed concerning the election of the detection of resistance mutant after serial passages. What we obtained is that we studied Telithromycin. After 44 passages we only selected or obtained three strains, resistant with MIC of two to four microgram per mL with L22 mutations on the ribosomal protein. There work was done in comparison with macrolide Erythromycin and Clarithromycin. We obtained -- we select mutation or mutant after five to 20 passages but the number of these mutant are extremely high and also the level of the MIC we obtained are different.

With Erythromycin or Clarithromycin or Erythromycin and also Roxithromycin, we did all the 14 and 15 available macrolides. We obtained MIC above

some time 32 or above 32 because there is a difference. So the number -- and so we have tested the frequency, the -- usually mutant will cure after one out of 10 to the seventh micro-organisms, with study is one to eight or one to the nine, so the frequency is low. The number of the mutant we obtained is low after a lot of cellular passages within 40 or more and also MIC we obtained four times the normal MIC or some time we have five times the normal.

DR. RELLER: Dr. Murray, do you have a follow-up question related to the resistance?

DR. MURRAY: Yes, I assume that was with an Erythromycin susceptible non-*erm* B containing strain. Were similar studies done if this background strain had *erm* B in terms of mutational frequency to resistance to Telithromycin or increased MICs?

DR. BRYSKIER: We did Erythromycin susceptible of course and also we tested -- or we did also this work with *mef* and with *erm* B. So with *mef* first we obtained also few mutants but increased MIC from all three or all six to all 25. With *erm* B we are selected also few strains but starting with an MIC, an extremely high MIC, for Erythromycin A. The work was done by Peter Appelbaum and we started with

MIC of above 32 and we have some strain with MIC of four. We have one with four and one with all three and as with one. So we obtained few. I cannot say no, also mutation on L22 and that is a very rare occurrence today in clinical setting.

DR. RELLER: Yes.

DR. MURRAY: Could you give frequency numbers as you did for the *erm* susceptible, one in 10 the sixth, seventh, eighth?

DR. BRYSKIER: Yeah, the work was done by Roland LeClercq in France and presented last year. I can't -- also it's 10 to the eighth or 10 to the ninth. It's very low.

DR. RELLER: Dr. Leggett had several questions related to resistance.

DR. LEGGETT: Not to resistance, just one question to resistance. Regarding a more clinical resistant pattern and regarding your desire for an indication for Penicillin resistant and Erythromycin resistant pneumococci, you stated the data of -- in your MM7 and other places, of 20 to 30 percent resistance and yet in the numbers involved, when you look at your trials of community acquired pneumonia, it's less than 15 percent. Can you explain the discrepancy between what the CDC is showing and what

we once again, when we're trying to look at this resistance indication, we can't seem to find them.

DR. SEIDLIN: I think this is a problem that the committee has experienced before with many submissions, that the number of patients with resistant pneumococci captured in clinical trials tends not to be representative of what's captured in epidemiologic studies in the population. I would, however, point out that our rate of identification of resistant pneumococci is relatively high compared to some other submissions. Indeed, we studied some 1300 patients treated with Telithromycin with community acquired pneumonia and had the numbers of isolates that you saw.

In contrast, my recollection is that for instance in the Levoquin submission there were many thousands of pneumonia patients in order to obtain some 16 resistance isolates. So I don't know whether that's a tincture of time with the increase of resistance out there in the world or we were extremely clever at placing our study sites or we were actually able because our enrollment criteria didn't try to select for patients with pneumococcal pneumonia. So I think that, yes, we didn't quite get numbers that were representative in the community but we did get

fairly respectable numbers for resistance isolates in this program.

The other point that I would like to make is that the numbers that I cited are sterile site isolates from the CDC and that's, of course, important because those are invasive disease and it's a good conservative number. Most studies that have looked at the incidents of resistance in respiratory secretions have been considerably higher. Numbers 18 to 35 percent have been reported in a variety of studies and in fact, our experience is consistent with that in that the rate of isolation of resistant pneumococci and sinusitis was relatively high.

DR. RELLER: Dr. Cross.

DR. CROSS: With regard to the adverse effects, in your presentation you lumped all the Phase III studies together. I was just wondering in the studies that looked at chronic bronchitis, a population probably enriched in older patients and those with underlying heart disease, was there any difference in the profile of adverse effects in this population?

DR. SEIDLIN: Dr. Leroy, would you present the adverse events in chronic bronchitis, please?

DR. LEROY: There was no major difference.

There was -- we can, yes, put the slide on which is the possibly related treatment adverse event in chronic bronchitis patients slide on. So you recall a rate of 13 percent in the presentation of diarrhea and in fact, it's almost less in this indication. It goes with the results that we've presented to you in elderly patients where the rates were a bit lower.

DR. RELLER: Dr. Ebert.

DR. EBERT: I have a similar question related to one of the other adverse effects, that being dizziness. Were there any demographic characteristics of the patients who experienced dizziness that would have predicted that they would see the side effect or was it related to the timing of the dose, for example?

MR. LEROY: I think that for the last question, the relation to the time and the dosing it was well addressed in Phase I, as you know, we've conducted high/low studies in this program which is generally not done. So we've been able to see that the dizziness was related to the dose clearly. At three gram two, there was more dizziness than 800 milligram, and it was following the dosing and the next 10 hours following the dosing.

DR. EBERT: And I was just curious, were

those patients generally taken this fasting or were they taking it with meals or did that delay absorption similar to what's been discussed with Trovafloxacin or is delaying the absorption and perhaps, minimizing the dizziness that's seen?

DR. LEROY: Okay, I understand your question. We've not studied exactly this question so I cannot answer exactly to the question. What we know is that the food interaction but Dr. Bhargava could elaborate on that. There was no difference in peaking the dose interaction. The nausea were a bit lower in Phase I when given -- when the product was given with food. We did not see any difference in dizziness but there was not a system of recordation so we cannot answer with certainty to this question.

DR. RELLER: Dr. Leggett, did you have another question?

MR. LEGGETT: Yeah, I have a couple of related questions concerning your proposed break points on page 70 of the book that you showed us in terms of susceptible and resistant, tying that in with the peak concentration levels and the AUCs that you listed and especially if you're looking at the Phase I, the QTc intervals and look at like 5,000 -- I don't remember which slide it was but there were several

thousand concentration points.

I notice that very few of them were above four. At least a half or more of your peak concentrations were less than two and yet, you weren't a break point that is four for the H. flu and I'm wondering a little bit about that especially in relationship to the 60 percent efficacy that you showed in, I believe it was the ABSSSI trial. In that regard, I wonder, looking at Craig's data, in his thing on page 222, it looks at the AUC to MIC ratio and the static point is someplace between 125 and 250, it looks like, looking at that trial.

If you take your AUC and divide by the MIC of the dose, to me it looks like your break point should be about .25 or .5 at the most rather than two or four, so I have a question about that. Related to that also, what in his mouse model, what was the peak to MIC ratio that corresponded to that static break point as well? And I say that in regards to many of the peaks with the telithro not getting to 4 and staying at one or two.

DR. SEIDLIN: Okay, there are several points in there and I'm going to try to remember them all so that I can touch on them. The first thing I'm going to talk to is the distribution of plasma

concentrations observed. Then we're going to talk about the AUC/MIC for S. pneumo and then we'll talk about H. Flu, okay? Let's see if I can remember all that.

Okay, the concentrations that were shown were not all obtained at peak. We requested that they be taken, I believe it was one to two hours after dosing but there was a distribution. The important point there was we were trying to correlate the serum level with the ECG findings and the serum level and ECG findings were within 1 hour of each other.

We can show you, if you like, the distribution of the time points for those levels. But those levels did not necessarily represent Cmax. For some patients, in fact, they did but not for all. All right, now turning to the AUC/MIC for S. pneumo. I think it's important to distinguish S. pneumo from H. flu in this context. Clearly, Dr. Craig's model is a S. pneumo model and it's really a systemic infection model where blood levels are quite important and I'm going to call up on Dr. Craig in a moment to detail those results.

For H. flu there is no good model to predict AUC/MIC and as Dr. Leroy mentioned earlier,

this is very much a tissue based infection. It's rather unusual to detect H. flu in the blood. So no AUC/MIC criteria for efficacy against *Hemophilus influenza* have really been developed from a model based method. Indeed, what we can do is we can look at the MICs of the H. flues isolated in clinical trials and the clinical outcomes to see if there is a correlation. Dr. Leroy, would you like to present that data, please, and then we'll go back to the S. pneumo.

DR. LEROY: If we look for example at community acquired pneumonia, we can see that -- we can see that -- so the number of pathogens both 4 is limited so we cannot conclude on that but we do not have a cut-off point from this data for its influencing community-acquired pneumonia.

DR. LEGGETT: And so as another follow-up question, I was going to ask about AECB but I'll ask it about here. Most of the time in upper respiratory tract infections, H. flu is cleared at least 50 to 60 percent of the time with a placebo. So looking at these rates, I'm a little nervous and I wondered what that placebo rate or if it's been tried, if you can tell me. In my recollection, it's pretty high for acute exacerbations of chronic bronchitis making these

numbers of 80 to 90 not necessarily as impressive.

DR. LEROY: Yeah, I think in those patients with community-acquired pneumonia one important point is that some of these patients had relatively severe pneumonia. So they may be cleared. We have also analyzed the fact to say that only single pathogen infections and patients with a single pathogen infection associated with a concurrent gram stain to try to see if there was a difference, and there was no difference.

The number are smaller if we can see these numbers. Certainly influencing community-acquired pneumonia is a question, the causality is a question, that's why we -- the next one, the one with the concurrent strains. Keep going. Okay, in any case, the number for the concurrent and gram stains showed a good efficacy around 80 percent. So we can see this one, slide on, which shows the number with a single pathogen, infection and a single and mixed infection. It was variable between the studies and if we can have the number with the -- we have also analyzed the concurrence gram stain, which is interesting to have, also 9, where we lose probably 20 percent of the single pathogens who had -- who had not a concurrent gram stain that is to say were not gram-positive or

gram stain and had also a good cure rate. Yes, slide on.

So these are the single pathogen infections with gram-positive on the gram stain. So when we tried to narrow down to a pathogen that we can consider more causative, we have the same type of rate.

DR. LEGGETT: Can you explain to me the mechanism of bacterial eradication in that highest group of the H. flu where not even the peak levels reached that amount?

DR. SEIDLIN: We believe it's due to the levels that are present in the extra cellular fluid and in the tissue. Dr. Bhargava showed you levels of 14.9 in ECF from Dr. Wise's lab and those probably account for the excellent outcomes.

DR. LEGGETT: But that's at the two to three hour level, right?

DR. SEIDLIN: Right, and they were actually sustained for quite awhile. Okay, shall we go to Dr. Craig?

DR. CRAIG: The drug has significantly different binding in animals than it does in humans. It has higher binding in animals and so we needed to focus on free drug levels. And so when we start

focusing on free drug levels, then the AUC to MIC ratio falls further. And then another thing that is quite clear with these drugs is also clear with flouroquinolones is that the white cell has a marked effect on the area under the curve that's required for efficacy.

So that when we look at those strains that we have been able to look at in normal mice or in special CBAJ mice where we, again, don't have to make them neutropenic, we're getting down to AUC to MIC ratios in the range of about 5 to 10 that's required. And when one takes those kind of values, then looks at the free drug ratio that one sees in humans, then one starts getting much higher break points, probably not up to 4 but up to at least 1.

DR. RELLER: Dr. Ebert.

DR. EBERT: Just a clarification regarding the sinusitis studies; were any of your sinusitis studies double-tap studies so you were able to look at eradication. I'm particularly interested in that because you're saying that the 5 day and the 10-day courses are equivalent and I wondered whether you had any microbiology data to support that.

DR. SEIDLIN: No, we do not. As you know, doing double-tap studies is rather a formidable

challenge.

DR. RELLER: Dr. Leggett.

DR. LEGGETT: A follow-up on the sinusitis studies, any ideas about in your comparator groups with the amoxicillin arm? In your PPb people there were only like four percent of bacteria that were actually isolated whereas in the other telitrho and the cefuroxime group there were up above 40 percent. Why the variability?

DR. SEIDLIN: That's because the first study which just compared five and ten days of therapy was a sinus puncture study in all patients and the third study there was the option of either sinus puncture on endoscopy. The study you're referring to was a clinical study so there were no bacterial isolation there.

DR. RELLER: Yes, Dr. Sumaya.

DR. SUMAYA: It appeared from the date presented that the resistance strains clustered around those patients that had community-acquired pneumonia as well as sinusitis. Is that correct and also was there any clustering in predictor H groups from the resistant strains?

DR. SEIDLIN: One would expect to see the most streptococcus pneumonia and pneumonia and

sinusitis. It is an important pathogen for AECB but other pathogens begin to play a more important role so that's not particularly surprising. Do we have an age distribution of the resistant pathogens? I don't recall that off-hand, but perhaps we could address it after the break.

DR. RELLER: We need to conclude very shortly but I have two closing questions. Dr. Murray has one as well. Dr. Murray.

DR. MURRAY: Actually, I'll ask perhaps that it be answered in the afternoon because you may need -- perhaps you can put the information together on a slide. I do have some concern about resistance emergence in the isolates that have *erm* B and I think there have been some abstract -- data presented in abstract form that suggest quite a considerably higher rate of emergence or resistance by plating *erm* B containing strains onto telithro containing agar.

With that background, there are two things that I've noticed that I would be interested in hearing comment on. One was an animal model published in January in JAC showing lack of efficacy against one of the *erm* containing strains and perhaps there's an explanation for why that was lack of efficacy. Bill may have hit upon it. If there's higher binding in

animals but they humanize blood levels but I don't believe they were free drug levels, so I'd like a comment on that. Perhaps that one would be quick.

But what I'd like perhaps to see a slide of is some of the data that were given in here on page 32 about animal results with Erythromycin resistant and it doesn't really allow me to compare either the ED50 -- the way it's written out. I'd like to see a table that says this was the Erythromycin susceptible, the Erythromycin resistant, the two mechanisms and what were the comparators -- comparative decreased in count and I can't pull that out of here. I'm given an ED50 for Erythromycin susceptible, but then for the Erythromycin resistant, I'm just told log decrease. So I can't really compare those internally and if it would be possible, I'd like to see that in a slide.

DR. SEIDLIN: Okay, we will certainly make an effort to get that together for you after the break.

DR. RELLER: Dr. Wald, did you have a question?

DR. WALD: I was just curious, in your high risk populations, patients with liver disease, the elderly and the kidney patients, what was the

range of the peak concentration of Telithromycin, because it seems to me there are relatively few patients in each of those groups.

DR. SEIDLIN: So you'd like to see -- remember these are not always peak concentrations but we can certainly show you the measured concentrations in those populations or we can go back to the Phase I data and look at those again. Which would you like to see? Do you want to see the Phase I or the Phase III?

DR. WALD: I wanted to see the peaks.

DR. SEIDLIN: Okay, so that's Phase I. Dr. Bhargava.

DR. BHARGAVA: I think the three that you're ask in terms of the hepatics, we had I said earlier, even the multiple dose situation at steady state almost no change in the peak levels and the peak levels are approximately 2.2 microgram per ML, so that would be the same in the healthy volunteers as well as hepatics.

In the elderly, as I showed in the Phase III, we did have a significant number of CAP patients where we connect -- collected serial pharmacokinetic samples up to six samples per patient and in that again, I was able to show that when you compare the less than 65 patients to the over, there's about a 20

percent increase in the over 65, so it's a 1.2 ratio and I think that last population you asked about was the renal population and in the moderate to severe impairment, we see approximately a 1.5 full change in the Cmax, so it would go from about 2.3 to 1.5 full higher than that.

DR. WALD: I was interested in the range rather than the mean.

DR. BHARGAVA: Okay, those were the means and when we looked at the ranges in the hepatics in fact, the range was very tight. So the outliers, in fact, were -- in our Phase I programs were no more than 6 so the highest, I think was about 6.5, 6.6 in all of our Phase I studies. So it's about, you know, two and a half to three-fold.

DR. RELLER: In the presentation emphasizing activity against Erythromycin A resistant streptococcus pneumoniae, there was an implication of lack of effective methylation efflux mutation and yet a couple of slides later, on M22, there was a shift in the MIC90 in organisms that had -- pneumococci that had these mechanisms. What's the explanation for the shift up in MIC90?

DR. SEIDLIN: There is some shift in MIC90 in the *erm* containing strains but still well within

the sensitive range. Clearly, in *erm* resistant isolates instead of the two binding sites on the 23SRA there's only one and it's still effective but not as -- the MICs do go up a little bit. For the efflux mutants, the -- as Dr. Bryskier pointed out, there is less affinity for the pump with Telithromycin than with Azithromycin, Clarithromycin, Erythromycin. However, the pump still exists and does pump out a little bit of the drug. So, yes, some does see a slight change in the MIC but it's well within the sensitive range.

DR. RELLER: And secondly, there's discussion of the activity with other potentially effective agents for resistant pneumococci. Could you comment on what data you have for Clindamycin activity versus Telithromycin activity in Erythromycin A resistant strains of pneumococci?

DR. SEIDLIN: Okay, I'm going to ask Dr. Bryskier if he has any data on Clindamycin to share.

DR. BRYSKIER: I want to ask you, do you want to know what's happen when you have a Clindamycin susceptible and resistant strain and phenotype or an *erm* B phenotype or genotype?

DR. RELLER: Well, I think in clinical terms and in the laboratory that an Erythromycin-

resistant pneumococcus, pediatricians, Dr. Wald, others, may comment on this, many of these strains are susceptible to Clindamycin. And I just wanted to know where this agent fits into the whole scheme of things relative to mechanisms of resistance compared with Telithromycin when one looks at what the options are available for therapy in patients who either cannot get Penicillin or have resistant strains to some of the other agents.

DR. BRYSKIER: Okay. When you have an MLSb mechanism, for instance, and an *erm* B or methylase usually Clindamycin is not considered as active so the second is when you have Clindamycin susceptible and I will say Erythromycin resistance, that's an m phenotype. For S. pneumo today when you have I would say *mef*, that's m phenotype Clindamycin susceptible, Erythromycin resistant for S. pneumo, Telithromycin MIC remain in the range of I would say 01 to 025, but what's most important, there is not really correlation between MIC of Telithromycin and the underlying mechanism of resistance to Erythromycin A for S. pneumo. You can have MIC of 05 and a *mef* but you cannot install an MIC of 05 with an *erm*. So there is no real correlation.

I will show you -- may I have the slide?

On this slide, that is a population distribution, for the strain, we collected of pre-clinical trial. You can see easily -- we can see easily that whatever MIC you obtain. So 002 up to 1 you can have resistant strain to Erythromycin or susceptible to Erythromycin, so there's no correlation. The same work was done with different gene and also you have no correlation.

For instance, now we know some time you could have a mutation on the [illegible] on the loop, on the peptidyl transferase, for instance we have one strain now with a mutation in A2049 and we still have a good ATt of [illegible]hromycin. So there is no real correlations between the gene, Erythromycin resistance, or susceptibility.

DR. RELLER: We will reconvene promptly at 1:00 p.m. after the lunch break. A quick reminder to the members and guests, there's an area in the restaurant that's been reserved for you, okay, so that you can come back promptly. Thank you.

(Whereupon, at 12:05 p.m. the above-entitled matter recessed, to reconvene at 1:00 p.m. the same day.)

A-F-T-E-R-N-O-O-N S-E-S-S-I-O-N

(12:59 p.m.)

DR. RELLER: Back to the afternoon session. There were a few residual questions, additional data that were left from this morning and I should like to suggest that we handle those after the FDA presentation during the time of the questions and discussion just before the break and then immediately after the break, we'll -- the committee will address the questions posed by FDA.

The FDA presentation will be started by Dr. George Rochester, who will present the FDA's assessment of clinical efficacy of Telithromycin.

PRESENTATION OF DR. GEORGE ROCHESTER

DR. ROCHESTER: Good afternoon. I am George Rochester, a clinical statistician with the Division of Anti-Infective Drug Products. I'm George Rochester, a clinical statistician in the Division of Biometrics III, co-located with the Division of Anti-Infective Drug Products and I will be presenting an overall summary of the clinical efficacy for this application.

We have heard the sponsor's presentation this morning which was quite detailed and our analysis at this point in the game are essentially identical in

most aspects of clinical efficacy, so I will not be going over all the details that were presented this morning but just the essential components and making some brief comments.

In order to look at the clinical efficacy, we want -- I want to create for you a basic framework within which we will present our viewpoints and information and characterize the importance of safety as well as efficacy in terms of determining risk benefits analysis for this product. Following my brief presentation, Dr. Alma Davidson will speak to the issue regarding resistant *S. pneumonia* and erythromycin resistant pathogens in terms of the indications that are being sought.

And then Dr. David Ross will talk about the overall general safety profile of Telithromycin with specific emphasis on QT issues. Dr. Edward Cox will then follow to talk about the hepatic effects and then we'll have a summary from Dr. Ross again about the risk/benefit profile of this drug.

To outline my talk, I will generally talk about the Phase III clinical data base, mention something about data that was censored from the Phase III clinical trials, clinical or bacteriologic efficacy and my talk will be mostly on clinical and

not bacteriologic except the tonsillar pharyngitis indication is actually a bacteriologic end point and followed by an overall conclusion.

The Phase III clinical data base essentially consisted of 13 Phase III clinical trials for four indications; community-acquired pneumonia, acute exacerbation of chronic bronchitis, acute maxillary sinusitis and a Group A beta-hemolytic streptococcus tonsillar pharyngitis.

Essentially, across all indications we've got at least two control trials for every indication. I will be mostly focusing on the information that comes out of the controlled trials rather than the uncontrolled situations and for all these studies, some of them were conducted including U.S. patients but there were no studies that were based solely in U.S. patients, so I did not use the terminology, U.S. studies.

Also there are subtle differences from time to time in terms of populations, maybe the types of patients that are included, even though essentially all CAP patients, enrolled patients with CAP, but we have difficulty in just making -- pooling such results and making all studies being equal into -- being poolable. So from out viewpoint, we will present

results with each study just being considered as it is and an overall summary of that information.

Essentially, a few sites were censored based on FDA investigation of clinical trial conduct, quality of data that was received for this Phase -- for the entire application. For the data that was submitted initially, for the first submission which was a year ago, there were four investigators that were censored by the FDA. And these investigators essentially were participants in other studies, other applications, not in Aventis that had some problems in terms of their data quality and data integrity and those investigators were then further looked at in relation to this application.

Those four that were censored accounted for a total of 186 patients and these patients were then excluded from all -- some were excluded from all indications except tonsillar pharyngitis and we excluded them from all our analyses and so did the sponsor and the sponsor agreed with us in terms of censoring this data. Phase III trials, the dosing of interest for three indications; acute exacerbation of chronic bronchitis, acute maxillary sinusitis and tonsillar pharyngitis was essentially for five day therapy and community-acquired pneumonia for seven to

10 days.

All studies had a designated test of cure window and had a similar design structure across all these indications and, of course, the test of cure window could vary in terms of a few days plus or minus, depending on which indications you are describing. But those were always pre-specified in the protocol and essentially were followed.

The primary efficacy populations for community-acquired AECB and maxillary sinusitis are both the mITT and PPc and contrary to probably popular belief, many people kind of assumed that we're only interested in looking at the per protocol -- clinical per protocol population but in fact, we do -- are always interested in the mITT analysis as well. So in my presentation, I will present both of those numbers.

The mITT population is defined as all randomized subjects who met disease definition based upon clinical presentation history, bacteriologic and/or radiologic information and received at least one dose of study drug will be included in the mITT population. And this is a modified ITT because patients could be excluded only based upon baseline characteristics. Patients were not to be excluded based upon something that transpired during the course

of the trial and that definition was used both by the sponsor and by us.

The mITT as well, that population, allows us to have two clear categories; you're either a failure or a success. There are no intermediate categories into that population. The protocol group, however, includes all mITT subjects minus those with major protocol violations and major protocol violations were always pre-described in the protocol ahead of time.

For community-acquired pneumonia there were essentially three clinical control trials; Protocols I, 6 and 9. The first one comparing Telithromycin to Amoxicillin, essentially had about five percent, 90 percent for comparator and 95 percent cure rate for Telithromycin. The second study, which -- in the protocol population. The second study which compared Telithromycin to Clarithromycin was about equal at 88 percent cure rate. And in Protocol Number 9, which was comparing Trovan, that one had 90 percent for Telithromycin and about 94 percent for Trovan, and of course, the sponsor did explain that that was a study that the -- when Trovan was restricted, that study continued as a single arm study later and so did -- the numbers in this study are a

bit smaller.

What we notice is that the 95 percent confidence intervals for both the PPc and mITT were within a 15 percent margin and if we exclude the study 3009, the other two studies fell within a 10 percent margin.

Acute Exacerbation of Chronic Bronchitis; to be included in this trial one of the essential features was that subjects needed to have a documented history of chronic bronchitis and at least in Protocol 3003, there was an FEV1/FVC ratio of less than 70 percent that was used to capture patients with certain severity of illness and these tests had to be made within the previous 12 months prior to enrollment in the study. At a time of presentation, subjects were expected to have increased cough, increases sputum volume, increased sputum purulence and/or dyspnea. And cure was defined as resolution of all signs and symptoms and no subsequently antimicrobial therapy could have been administered prior to the test of cure date. In this study we did notice that even though I'm not discussing details about the bacteriologic efficacy, that in fact, most of the patients here, the most common pathogen was *Hemophilus influenza* and not *S. pneumonia* as one might expect from the literature.

In these two trials we see again, both the PPc and the mITT populations that the rates were somewhere ranging from 83 to 86 percent, similar for comparator as well as Telithromycin and the integral bounds in these confidence intervals were within the 10 percent lower bond margin that we've established to declare therapeutic equivalent.

For acute maxillary sinusitis, this is -- we're looking at the five-day of Telithromycin that compared to 10 days and in study 3005 there were two clinical -- two controlled studies here. In study 5 this result is only for the five-day arm compared to the 10-day arm. It was 10 days of comparators. It was a 10-day arm and a 10-day arm also met our confidence integral bounds of declaring equivalence. Both the mITT and the PPc and the mITT populations here showed fairly consistent results in terms of confidence intervals that we expected to see.

One should note, however, in study 3005 the five-day, a rate of just 75 percent consider it the natural history of that disease and that patients were also allowed during this protocol to have concomitant use of -- concurrent use of medications such as antihistamines and antipyretics, inflammatory medications. So, therefore, one should just bear in

mind that the 75 percent cure rate itself is not necessarily that great. However, these results seem fairly consistent from among the two trials. In the second study, 3011 in that study the population was restricted to by case definition, to include most of the subjects who had at least seven days of symptoms at the time of enrollment while in the first study, that was not clearly the case and in fact, approximately 40 percent to my recollection, of subjects in that study presented with signs and symptoms that were within the seven-day window when one may suspect there is a high possibility of viral infection as opposed to bacterial sinusitis.

However, those differences were equal for both treatment arms. So both populations pretty much had about the same occurrence of both characteristics.

For the Group A beta-hemolytic streptococcal tonsillitis/pharyngitis, we want to make some basic comments, very few comments on this, regarding this indication and that when we're interpreting in the regulatory context our findings of efficacy, simply meeting a statistical criterion that you are within your minimum confidence interval bounds, is a minimum criterion that is usually necessary to meet but it is in no way sufficient in

terms of for a drug to win. And there are other considerations that should be borne in mind.

For example, in this indication, penicillin is still the gold standard that we expect as a comparator and the primary efficacy for this is based upon microbiologic eradication and not necessarily just clinical impressions. And any product with an absolute eradication rate of less than 85 percent and the protocol population should not be considered first line therapy. And this is certainly within the spirit of the guidance that has been on the web for some time.

Tonsillar pharyngitis is also a mild diseases. A targeted population is typically children. There are many alternative therapies that are currently available for this indication. There was insufficient evidence of activity against Erythromycin resistance strep pyogenes and the risk benefit ratio must be considered very carefully in terms of when we put a drug on the market whether or not there is truly a benefit that outweighs the risk before it's approved.

Our overall conclusion is that FDA's efficacy analyses are consistent with those of the applicant's computationally and, of course, we do take

other considerations into mind when we make conclusions about the utility of these numbers. And that adequate well-controlled trials must demonstrate both safety and efficacy in order for a drug to be approved to market. So I would then like to turn it over to Dr. Davidson, who will now continue the presentation and talk about the resistant pathogens.

DR. RELLER: Dr. Alma Davidson.

PRESENTATION OF DR. ALMA DAVIDSON

DR. DAVIDSON: Good afternoon. My name is Alma Davidson. I'm a med officer with the Division of Anti-Infective Drug Products and I will focus my presentation on the applicant's proposed drug resistant streptococcus pneumonia claims of Telithromycin. This is the overview of my talk which includes at the outset I will present the applicant's proposed labeling for resistance of Telithromycin. Then I'll talk about Penicillin resistant streptococcus pneumonia claim, including a brief review of regulatory history of selected antimicrobial agents which were previously presented before the advisory committee.

Next, I will review the Erythromycin resistant streptococcus pneumonia claim. I will make summary comments at the end of each section. I will

be referring to the acronym PRSP for Penicillin resistant streptococcus pneumoniae and the acronym ERSP for Erythromycin resistant streptococcus pneumoniae in my subsequent slides.

This slide displays the applicant's proposed labeling for resistance claims, community-acquired pneumonia and acute sinusitis due to streptococcus pneumonia including strains resistant to Penicillin G and Erythromycin A. Now I will consider Penicillin resistant streptococcus pneumoniae claims beginning with the review of issues discussed by previous advisory committee and the regulatory history of selected antimicrobial agents.

The previous advisory committee considered several issues regarding potential resistance claims. Foremost was the seriousness of the disease, for example, meningitis and bacteremic pneumonia. Much of the previous discussions focused on community and hospital acquired pneumonias. In general bacteremic pneumonia carries a higher mortality rate and is a sign of invasive disease. In addition, documentation of a pathogen in the blood which is a sterile site, add certainty to the diagnoses. It was felt that an applicant should demonstrate efficacy for resistant pathogens in serious disease prior to claims and less

serious indications.

Next the strength of evidence to support the proposed resistant claim for antimicrobial agent was discussed. I will review some of the data in the subsequent slides. Another issue is the relationship of the mechanism of resistance -- of the resistant pathogen to the mechanism of action for this agent being considered. These issues will lead to different considerations. For example, the so-called out of class agents such as the treatment of PRSP with quinolones or within class agents such as Agumentin. Finally, what is the impact to public health of such a claim.

For the remainder of my presentation, I will consider only community-acquired pneumonia indication, especially bacteremic community-acquired pneumonia as it represents a serious invasive type of disease. I will now review data which was discussed at the previous advisory committee meetings for Levofloxacin, Moxifloxacin and Linezolid.

This slide reflects the information that the advisory committee considered when reviewing Levofloxacin for the indication of community-acquired pneumonia with a PRSP claim. Within the MDA data base, a total of 250 -- 250 microbiologically

documented cases of streptococcus pneumonia community-acquired were studied with a 98 percent success rate. Of this, 15 cases were due to PRSP with 100 percent cure rate. There were 55 cases of bacteremic pneumonia due to streptococcus pneumoniae with 100 percent cure rate. The susceptible cases and the resistant cases both had 100 percent cure rate.

Following from the data we just presented to the agency and the advisory committee, Levofloxacin was granted an indication of community-acquired pneumonia with PRSP claim. The text of the current label follows. "Community-acquired pneumonia due to streptococcus pneumoniae (including Penicillin-resistant strains) MIC value for Penicillin was greater than or equal to two micrograms per mL".

Now, let's turn over to Moxifloxacin. As we can see, the total experience for community-acquired pneumonia due to streptococcus pneumoniae was 89 cases with a 90 percent cure rate. In this application, only one study, Study 140, collected blood cultures from which the streptococcus pneumoniae was isolated. In this study six cases were due to PRSP, 10 cases had documented bacteremia and only one or two of them were due to PRSB. The Moxifloxacin label does not carry -- currently carry a claim for

CAP due to PRSB.

Let's turn over to Linezolid. Here the applicant collected a total of 100 cases of CAP due to streptococcus pneumoniae with a cure rate of 88 percent. It is important to note that out of the 33 bacteremic cases, none were due to PRSB. The Linezolid label carries an indication for community-acquired pneumonia and specifically states that it is not to be used for PRSB.

Moxifloxacin and Linezolid were not approved for PRSB claim and the indication of community-acquired pneumonia due to insufficient evidence upon which to base this claim. Now, let's review the Telithromycin data submitted in support of PRSB claims for community-acquired pneumonia. This is a summary of data across controlled and uncontrolled studies. Less than five cases were documented among the comparator group. This slide shows that the total number of patients with documented streptococcus pneumonia isolates regardless of susceptibility was 174 with a clinical success rate of 96 percent. Of this 17 were due to PRSB. There were 38 cases of bacteremic pneumonia with a cure rate of 89 percent, compared to 67 percent among PRSB cases. It should be noted that there were only six case of PRSB

bacteremia.

If we compare this experience to Levofloxacin, we note that the evidence is somewhat smaller with lower clinical cure rates among the bacteremic cases, especially PRSB. In summary for Telithromycin treated patients, the overall clinical success rate of community-acquired pneumonia due to streptococcus pneumoniae was 82 percent among 174 cases. Seventeen cases of PRSB and community-acquired pneumonia were documented. The majority of patients had mild to moderate pneumonia based upon fine scores. Two of the failures had severe infections with PRSB and were treated in the hospital setting. The other failure had a moderately severe infection and was also treated in the hospital.

There were six documented bacteremic cases of PRSB pneumonia with a cure rate of 67 percent. Bacteremic failures occurred in sicker populations. They both required hospitalization and additional intravenous antibiotics.

Now, let's switch gears to Telithromycin and Erythromycin resistant streptococcus pneumoniae claim of Telithromycin. This slide summarizes the clinical success of Telithromycin for ERSP claim and community-acquired pneumonia. You will notice that

these numbers are identical to the numbers for PRSB cases. However, they are not the same patients. There are about 50 percent concurrence in cases of PRSB and ERSB. Again, the overall number of documented ERSB pneumonia cases was 17 with a cure rate of 82 percent. Likewise, the cure rate among the bacteremic ERSP cases was 67 percent.

Now, since the *mef* E genotype is the most common type in the United States, isolates carrying this gene will be considered in the subsequent slide. This slide summarizes the Telithromycin and Erythromycin MICs in community-acquired pneumonia with the *mef* E genotypes. The first column indicates the MICs of Telithromycin. The second column indicates the MICs of Erythromycin and the third column is the number of cases with the *mef* E genotypes and their data base.

Interestingly enough, as the MICs of Erythromycin increases, the MICs of Telithromycin also increased. You will recall that the applicant's proposed break point of Telithromycin sensitivity is greater than or equal to 1 microgram per mL. Although the number of isolates with the *mef* E genotypes are small, this observation of increasing MICs Telithromycin may raise the possibility of potential

concurrent resistance between Telithromycin and Erythromycin or macrolides.

Finally, summarizing the Erythromycin resistant streptococcus pneumoniae experienced in community-acquired pneumonia. There are 17 documented cases of community-acquired pneumonia with ERSP with a cure rate of 82 percent. All three failures had a concurrent Penicillin resistance. Two of the failures had *erm* B genotypes. Six bacteremic cases with ERSP had a cure rate of 67 percent. Will cross resistance or concurrent resistance between Telithromycin and Erythromycin clinical isolates occur? That is the question. Dr. Ross will further consider this prospective of risk benefit assessment in his summary discussion at the end of the FDA discussion.

This ends my presentation. Thank you for your attention.

DR. RELLER: Dr. David Ross.

PRESENTATION OF DR. DAVID ROSS

DR. ROSS: Good afternoon. My name is David Ross. I'm in the Division of Anti-Infective Drug Products at FDA. I'm going to speak about the general safety profile of Telithromycin, followed by discussion of its cardiac effects. Dr. Edward Cox will follow with a discussion of hepatic effects of

Telithromycin followed by discussion by Dr. Zachary Goodman of drug induced liver disease and then we'll finish with an overview of risk benefit issues.

Let me start by summarizing the Ketek Phase III safety data base. There were 4,985 patients who received at least one dose of Ketek or comparator. Forty-eight of these patients did not have post-baseline safety follow-up information leaving 4,937 patients in the safety data base, 3265 Ketek, 1672 comparator. In the nine control trials, there were 2,045 Ketek treated patients and 1,672 comparator treated patients. In the four uncontrolled trials, there were 1,220 Ketek treated patients.

In terms of extent of exposure for patients who were treated with the five-day regiment, there were 1,429 patients and as you can see the mean exposure was about five days. For patients who are receiving regiments of seven to 10 days or 10 days, there were somewhat over 1800 patients in this group. Mean exposure was about nine days and for the entire data base of Ketek patients, mean exposure was about seven days. Mean treatment time for comparators was a little under 10 days.

With respect to deaths, there were no deaths in Phase I trials. There were 11 deaths in

Phase III trials, 10 of these were in CAP trials, 1 in a tonsillar pharyngitis trial. This was a comparator treated patient who died of acute lymphoid leukemia. There were seven deaths in Telithromycin treated patients, four in comparator treated patients. None of these were directly attributable to drug. Six of the deaths, four in Ketek, two from comparator treated patients were scored as treatment failures.

With regard to primary or secondary causes of death, six out of seven Ketek treated patients who died had a cardiovascular cause, zero out of four comparator treated patients who died had a cardiovascular cause. Most of the CAP deaths occurred in patients who were at high risk for morality, that is Fine Category III or higher.

With respect to serious adverse events, this table shows SAEs in controlled trials, there were 40, that is two percent in Telithromycin treated patients and 41, 2.5 percent in comparator treated patients. The remainder of the table shows serious adverse events that were possibly related to treatment and these are listed here.

In the uncontrolled trials there were four SAEs that were possibly related to drug. These occurred in Telithromycin treated patients and

included gastroenteritis, vasculitis, hepatitis and leukopenia. With regard to adverse events in the controlled trials the most common adverse events were gastrointestinal such as diarrhea, nausea, vomiting, dyspepsia, abdominal pain or abdominal LFTs as well as nervous system, headache, dizziness and blurred vision with was a special senses adverse event. For diarrhea, as noted previously, the rate was higher in controlled trials than in comparator and blurred vision has also been noted. These were predominantly younger women in tonsillar pharyngitis trials. In one case, the episode of blurred vision lasted for several days.

Because Telithromycin is metabolized in part by the 3A4 system, it was of interest to analyze adverse events according to 3A4 inhibitor intake as shown on this slide. It should be emphasized that this is an exploratory analysis since patients were not randomized on the basis of 3A4 inhibitor intake. For the most common adverse events, most -- for example, for diarrhea, in general, there was a higher incidence in Telithromycin treated patients who received a 3A4 inhibitor compared to those who did not. In addition, the ratio of incidences between Telithromycin and comparator treated patients was

greater when patients received a 3A4 inhibitor than when they did not receive a 3A4 inhibitor.

My pointer is not working here. Let me move on to a discussion of cardiac effects of Telithromycin. I'm going to discuss the in vitro and pre-clinical data Phase I data submitted by the applicant, Phase III data submitted and then finish with conclusions. I want to just briefly speak to one issue which is the use of correction factors. In general, despite its limitations, QTc is the yardstick that we have used to detect signals indicating the potential for malignant ventricular arrhythmia such as Torsades.

Obviously, there's been a lot of work in terms of defining alternative correction factors. It's important to emphasize that these would need to be validated against an appropriate population. So for the remainder of my discussion, I'm going to focus on QTc. Let me start with the effects of Telithromycin on repolarization in vitro and in pre-clinical models. As has been noted previously, Telithromycin inhibits the Ikr channel which is the major repolarization current. The Ki or concentration at which inhibition is half maximal, is 42.6 micromolar. Lower Ki means more potent inhibition. You previously saw data for comparison that Moxifloxacin was 129 micromolar. You

can compare this to concentrations seen in Phase I studies, in Phase III studies. The mean serum Cmax was 2.4 micromolar, and this is total drug. The maximum observed concentration in Phase III studies was 12 micromolar.

It's important to remember that these relate to serum concentrations. In a rat study conducted by the applicant, the myocardium had a higher concentration than serum in a ratio of six to one. So concentrations in myocardium may reach those of the Ki. In other in vitro models, Telithromycin prolongs action potentials in isolated Perkinje fibers. At the Ki there was a greater than 75 percent increase in APD90 a measure of action potential duration. It's also important to note that in a controlled in vitro model, Telithromycin potentiates Sotalol induced APD prolongation.

Finally, in a dog model, Telithromycin prolonged the QTc and increased heart rate. After IV infusion, QTc was increased by 30 milliseconds within one minute compared to 17 milliseconds for Clarithromycin. After multiple oral doses, the increase was 27 to 30 milliseconds.

Let me move onto the Phase I studies. Telithromycin showed an effect on QTc increasing it in

both young subjects and elderly subjects, despite the entry of these rationally normal subjects not with underlying disease for both rows. The amount of increase showed dose dependence with higher increases at greater doses, 28 milliseconds at 2400 milligrams in young subjects, 19 milliseconds at 2000 milligrams for elderly subjects. All of these increases were statistically significant with respect to placebo.

In a study in changes in QTc in patients with underlying cardiovascular disease, at four hours after dosing Telithromycin at a dose of 1600 milligrams was significantly different than placebo. It's important to note that this peak effect occurred at four hours since the Tmax occurred at around 1.5 hours, plus the peak effect on QTc occurred after concentration peak was reached. I should note that one patient in this study had an episode of syncope. This was not felt to be related to cardiac dysrhythmia.

Results from Phase I studies pooled showed a lot of variability around the regression line but showed that there was a significantly different regression line from the mean, highly significant, with a slope of 3.9. In other words, for each milligram per liter increase in Telithromycin

concentration, one would predict a 3.9 millisecond increase in QTc. And it's important to remember that in terms of the range of concentrations that were seen or that were likely to be seen in clinical -- in the real world.

The applicant conducted a study in which Telithromycin -- the effects of Telithromycin alone, Cisapride alone, and Telithromycin plus Cisapride were examined. You will remember tat Cisapride is a 3A4 substrate that has been associated clinically with Torsades and other arrhythmias. As you can see, the curves for -- blue is placebo, green is Cisapride, yellow is Ketek and pink is the combination. As you can see, the changes in QTc for Ketek and Cisapride were comparable. When given together, the two had at least an additive effects on QTc. Because of the metabolism of Ketek by the 3A4 system, it was also of interest to see what the effects of concomitant administration of a potent 3A4 inhibiter, Ketoconazole were on both Telithromycin pharmacokinetics and QTc effects.

When Telithromycin and Ketoconazole were given together, the increase in QTc compared to placebo was about 10.5 milliseconds which was statistically significantly different from placebo.

In terms of the pharmacokinetics, administration of Telithromycin and Ketoconazole together increased the Cmax by about 50 percent. The AUC almost doubled. Because of the concentration dependence of Telithromycin's effect on QTc, it's important to understand factors that might effect Telithromycin concentration and therefore might effect Telithromycin's effect on QTc.

It's important to note that Telithromycin has non-linear pharmacokinetics. As the dose goes up, clearance decreases and this decreases our ability to predict what concentrations or other pharmacokinetic results will obtain with altered doses or exposures. At a single dose of 800 milligrams, the mean Cmax was around two milligrams per liter. However, the maximum Cmax was over five milligrams per liter and this occurred in the subject with renal impairment. In a multiple dose study of 800 milligrams, again, the mean Cmax was around two milligrams per liter. The maximum observed Cmax was 6.66 milligrams per liter and this occurred in an elderly subject.

In population PK studies in Phase III the maximum observed concentrations were 7.6 to 9.9 milligrams per liter. It is important to keep in mind in assessing these, that these were not necessarily

drawn at the peak at Tmax and plus may not represent true peak values. With regard to pharmacokinetics in special populations, elderly subjects in Phase I showed a doubling of Cmax in AUC. In subjects with hepatic impairment, in a single dose study, half life was increased by 40 percent. The applicant has conducted a multiple dose study. The final report from this study has not been submitted to the agency review as of this date but AUC and Cmax appear similar in healthy subjects. Although t-1/2 does not appear to be increased, because we have not had the opportunity to review this study in detail, we cannot comment on the reasons for this discrepancy.

What does seem clear is that renal clearance increases to compensate for hepatic impairment implying the potential accumulation of Telithromycin may occur if there's decreased creatinine clearance in the setting of hepatic impairment.

Finally, in a single dose study in renally impaired patients, in patients with moderate renal impairment, creatinine clearance of 40 to 80 milliliters per minute. The Cmax was increased by a third, AUC was increased by 42 percent. In subjects with severe impairment, creatinine clearance of less

than 400 mLs per minute, the Cmax was increased by 44 percent and the AUC was increased by 59 percent. Recall that these changes occurred despite the fact that renal clearance represents only about 13 percent of the total clearance of this drug.

So let me just summarize the results from Phase I and I want to just say that these analyses are the hard work of my colleague Dr. Jenny Zhang in the office of Clinical Pharmacology and Biopharmaceutics at FDA. Telithromycin showed a concentration in dose dependent increase in QTc. The QTc increase associated with Telithromycin was comparable to Cisapride and at least additive when the two were given together. The increase was enhanced by concomitant administration of a 3A4 inhibitor, Ketoconazole. The concentration of Telithromycin was also increased by a concomitant Ketaconazole administration. PK variability was seen in part due to non-linear pharmacokinetics.

There's the potential for increased exposure with age and renal impairment as well as the potential for increased exposure in hepatically impaired subjects with decreased creatinine clearance.

Let me change from the sort of clean world of controlled Phase I studies to the somewhat more

tricky issues involved in assessment of QT changes in Phase III. It's important to recognize that the clinical events that we're looking for that are associated with changes in QTc are rare. For example, with Cisapride there were no clinical events associated with prolonged QTc in the NDA data bases and as Dr. Ruskin pointed out, it was only after a large number of courses had been prescribed that a signal could be detected.

There is substantial variability in measurements of QTc. There are inter-individual measurement differences. There are differences between observers and there are differences for a given individual in measurement either because of biological variabilities such as circadian rhythm changes or for differences between measurements taken by the same observer and there are systems that have been described such as digitizing pads and the like for trying to minimize this sort of variability.

Finally, the significance of changes in QTC may not always be clear. Drugs that are associated with a small change in QTc may still be associated with Torsades. For example, the Terfenadine, which has a mean increase of only six milliseconds in healthy subjects, is well-known to be

associated with Torsades because of metabolic interactions. In addition, the increase in risk for a given increase in QTc is not always clear.

Let me mention, moving from these general caveats, let me mention some specific limitations of the EKG data in the Phase III data set for this application. EKG data was not collected on all patients. In controlled trials, there was EKG data from 1,515 Ketek treated patients, 1,276 comparator treated patients allowing calculation of changes in QTc intervals. There were relatively few data from high risk patients and this was in part because of the design of the trials in which there were multiple exclusion criteria that would have left out such patients. For example, in terms of patients with EKG data allowing QTc intervals to be analyzed, there were two Telithromycin treated patients with a baseline potassium of less than three.

There were five Telithromycin treated patients in the EKG data set who were on anti-arrhythmics. In addition, the number of patients with higher concentrations was relatively limited, decreasing the ability to analyze patients -- QTc changes in such patients. The timing of EKGs in the Phase III studies may not have corresponded to the

peak QTc effect. As I noted earlier, the peak QTc effect in a number of Phase I studies occurred at four hours. However, the protocols called for EKGs to be obtained at one to three hours after dosing. Thus the EKGs obtained may not have estimated the peak QTc effect.

EKGs were also obtained at different times after dosing further increasing the variability. EKGs were obtained at 25 millimeters per second. A number of studies examining QTc prolongation have used chart speeds of 50 millimeters per second to increase resolution. Finally, there was no data available on serum magnesium, hypomagnesemia is a recognized risk factor for Torsades.

This just shows some of the exclusion criteria for Telithromycin Phase III trials and these included conditions such as long QT syndrome, severe hypokalemia and a variety of concomitant medications. As Dr. Benedict noted previously, a number of these criteria were dropped part way through the development program. However, it's important to note that despite this, there still remain relatively few patients in some of these risk groups. For example, there were only six Telithromycin treated patients receiving Digoxin in the controlled trials.

For other drugs that potentially interact such as protease inhibitors, there were only three patients in the data base who received protease inhibitors. The analyses I'm going to show focus on the controlled Phase III trials. I will not discuss the uncontrolled trials. In order to control for variability, we've tried as much as possible to compare like with like. In the set of patients from all controlled studies for whom EKG data was available to calculate QT changes, on therapy changes in Telithromycin treated patients were two milliseconds. There was a net decrease of .7 milliseconds for comparators.

For the majority of the demographic groups analyzed, changes in the Clarithromycin were greater than those for comparators. We specifically compared Telithromycin with the macrolide used in these studies, Clarithromycin and we compared those trials in which there were Telithromycin treated patients compared with Clarithromycin treated patients, that is, studies 3006 and 3008. For all patients together, the magnitudes of the QTc changes were similar. However, they were slightly greater for female patients, 3.7 milliseconds for Telithromycin treated patients, 2.3 milliseconds for Clarithro treated

patients.

For elderly patients, the increases were 5.3 milliseconds for Telithromycin treated patients, 1.6 milliseconds for Clarithromycin treated patients. Because Telithromycin is metabolized by the 3A4 system, we analyzed QTc changes in patients who received concomitant 3A4 substrates as well as 2D6 substrates. Again, I'd like to caution that these are exploratory analyses since patients were not randomized on the basis of co-administration of these substrates. For Telithromycin, for patients who did not received a concomitant 3A4 substrate, the change in QTc on therapy was 1.3 milliseconds. For those who did receive a 3A4 substrate, it was 3.2 milliseconds. Both of these changes were greater than for comparator groups.

For those patients who did not receive 2D6 substrates the increase was 1.4 for Telithro, negative 1 for comparators. Again, receipt of a 2D6 substrate increased the QTc by 5.3 milliseconds for Telithromycin, 0.7 milliseconds for comparators. In patients who received a drug or drugs that were both -- that were 3A4 and 2D6 substrates, the increase for Telithromycin was 6.9 milliseconds, 3 milliseconds for comparators.

We performed the same analysis comparing Telithromycin with Clarithromycin and again, these are studies 3006 and 3008. Again, we saw the same pattern. If patients did not receive a concomitant 3A4 substrate, Telithromycin had a QTc increase of 3.1 versus 2.7 for Clarithromycin. If there was a 3A4 substrate, the increase was 4.1 versus 2.9. For patients who received concomitant 3A4 and 2D6 substrates, the increase for Telithromycin was 11.5, for Clarithromycin 5.4.

We also examined outliers, focusing particularly on individuals who had increases of more than 30 milliseconds. Looking at all controlled Telithromycin trials, the number of patients who had increases of 31 to 60 milliseconds for Telithromycin was 7.3 percent versus 5.7 percent for comparator. The difference is not statistically significant. A similar analysis for Telithromycin versus Clarithromycin showed 7.9 percent for Telithromycin, 6.8 percent for Clarithro, again, the differences are not statistically significant.

So let me summarize the conclusions from these data. Telithromycin inhibits repolarization in vitro both in the cell culture model looking at the IKR channel and isolated Purkinje fibers. Data from

a rat model suggests that the myocardial Telithromycin concentration may approximate the Ki for these effects. In a dog model, Telithromycin significantly increased QTc with both oral and IV dosing. The effect of IV Telithromycin was greater than that of IV Clarithromycin.

With regard to Phase I, Telithromycin increased QTc in controlled cross-over studies and this was a consistent effect. The effect was concentration and dose dependent. It was comparable to Cisapride and at least additive with Cisapride and increased by co-administration of 3A4 inhibitor. With respect to PK variability which might effect Telithromycin concentration and therefore, its QTc effect, Telithromycin shows non-linear pharmokinetics and showed increased exposure in special populations.

Finally, in Phase III Telithromycin increased QTc. This was a small but consistent effect. The increase was larger than with comparators, including Clarithromycin and exploratory analyses suggested possible interactions with 3A4 and 2D6 substrates. As an example in trials comparing Telithromycin with Clarithromycin, the mean increase for Clarithromycin with both 3A4 and 2D6 substrates was 11.5 milliseconds compared to 5.4 for

Clarithromycin.

Let me stop here and turn the podium over to my colleague, Dr. Edward Cox.

PRESENTATION OF DR. EDWARD COX

DR. COX: Hello. I'm Edward Cox. I'm a medical officer at the FDA. And I'll be providing the agency's presentation of the hepatic effects of Ketek. And just to give you an overview of my talk, first I'll talk a little bit about some of the pre-clinical studies with Ketek and then move on and describe some of the events in the Phase I studies in humans and then move on to the Phase III studies and discuss the hepatic adverse events as seen and then move on and talk about the analysis of laboratory data and then a discussion, a brief discussion of some of the serious adverse events that we're seeing.

And when I get to the point of describing the serious adverse events, I'll ask Dr. Goodman to come up and describe some of the histopathologic findings from one of the patients -- or from the patient who had a liver biopsy. And then after Dr. Goodman's presentation, I'll come back and just briefly summarize the findings from the hepatic effects.

And first, just to start out, with regards

to the pre-clinical studies, hepatotoxicity was seen in rats, dogs and monkeys and this hepatotoxicity was manifested as increases in AST and ALT. Hepatic necrosis was seen in the four-week rat study and hepatocellular hypertrophy and multi-nucleated hepatocytes were seen in some but not all of the pre-clinical animal studies. And our FDA pharmacology/toxicology reviewer had the opportunity to go back and review the original data that was submitted with the Clarithromycin NDA in order to be able to compare the effects seen with Telithromycin with that which was seen with Clarithromycin and the conclusion from the review was that the hepatic effects of Telithromycin were more than what was experienced with Clarithromycin.

And now what I'd like to do is just run through essentially a dose response curve from the Phase I studies in humans. And just to start out, I'll describe the layout of the table here for you. In the right most column we have the Ketek dose in doses ranging from 50 milligrams up to 3,200 milligrams and I've lumped some of the lower doses together here just to compact the size of the table.

We also have in the very bottom here, the data for those periods during which subjects received

placebo medication. In the middle group of columns here are the results from the single dose studies and then in the right most column are the results from the multiple dose studies. With regards to hepatic adverse events, I'd like to call your attention to this column here which shows the percentage of events that occur for any particular dosing period and if we move from low levels of dose up to the dose of 2,000 milligrams, we do see a clustering of events here at 2,000 milligrams. Then moving onto higher doses we do see somewhat of a fall-off.

With regards to hepatic adverse events in the multiple dose studies, we see that the events there were infrequent. I will describe some results from one of the Phase I studies, Study 1030 which included eight elderly subjects and who received doses up to 2,000 milligrams and this is the highest dose that elderly subjects received during the Phase I studies.

The study included single doses of 1200 milligrams, 1600 milligrams and 2,000 milligrams and then interdigitated between these doses was a placebo period. The doses were separated by approximately a one-week period of wash-out. There were three patients who achieved increases in ALT and AST with

levels ranging from approximately 100 to the levels of 300 with ALT being greater than AST. And these three patients, the first was a 72-year old female, who seven days after receiving a 2,000 milligram dose of Ketek, demonstrated an increase in her ALT and AST.

As part of her work-up for viral etiologies of hepatitis, this patient also had a CMVIGM that was positive. The second patient who in this particular study developed increases in ALT and AST, was a 69-year old male who 17 days after receiving the 2,000 milligram dose of Ketek experienced increases in his ALT and AST.

And the third patient is a 62-year old male who seven days after receiving a placebo which was also, because of the nature and design of the study, 14 days after that patient received a 2,000 milligram dose of Ketek, experienced increases in his ALT and AST and as part of the serologic evaluation for etiologies of hepatitis this patient had an EBVIGM that was positive. The -- the viral serologies that were done when looking at the full set of data available there, do not provide definitive evidence of diagnosis of a viral etiology and I think, you know, one of the other points to be made here is that this could represent a possible drug effect. In such a

situation, we'd be talking about a drug effect that would have a seven to 17-day latency period given the chronology of events here.

With regards to hepatic adverse event rates from the Phase III studies, the adverse event reasons that were experienced were similar for both Ketek and comparators. The rates for treatment continuation were similar for Ketek and comparators. With regards to serious hepatic adverse events from the comparative studies, there were two Ketek treated patients who experienced serious adverse hepatic events and one comparator treated patient who experienced a serious hepatic adverse event.

From the non-comparative studies there was one additional Ketek treated patient who experienced a serious hepatic adverse event. With regards to hepatic deaths, here were not deaths that were attributed to drug induced hepatic injury. And now before coming back and talking about the serious hepatic adverse events, I'd like to describe some of the laboratory evaluations that were carried out to -- within the Phase III studies. And I'll focus on evaluations from the comparative studies in patients who are normal at baseline for AST, ALT and T. bilirubin.

I'll look at essentially what are ladders of AST and ALT elevation and I'll only present data from the CAP studies and in the CAP studies there were more AST and ALT elevations at the on therapy and post therapy visits in the Ketek arm. For these corresponding time points in the non-CAP studies, Ketek and comparator were similar.

And I'll just run through the design of this slide. We're looking at AST changes that occur at the on-therapy visit which is day 2 to 5 in patients who are normal at baseline from the community-acquired pneumonia studies. And we're looking at changes in AST and the ladder here goes from those patients who have values of less than or equal to one times normal and then at intervals increasing up to a level of greater than five times normal.

In this column we have the results for the number and percentage of Ketek treated patients who achieve these levels of elevation, then for the comparator treated patients, similar with the number of comparator treated patients and the percentage of patients achieving that level. And what I'd like to do is to call your attention to this row here where the levels of elevation are between one times and less

than or equal to two times the upper limit of normal where we see a slightly greater proportion of elevations in the Ketek treated patients.

Now, again, a slide of very similar design. We're still looking at AST. However, this is at the post-therapy visit, so at day 17 to 21. We're looking at changes in AST and again, the same ladder for Ketek and comparator treated patients and if we look at the percentage of patients experiencing this level of elevation of one to two times normal, we see that six percent of Ketek treated patients achieve this level, whereas two percent of comparator treated patients achieve this level and we see a few events occurring at levels beyond the two times normal category.

Now we're moving onto ALT. We're back at the on-therapy time point of day 2 to 5 and so we're looking at changes in ALT again the same ladder and for Ketek treated patients and comparator treated patients, if we look at the same row that we've been looking at here between 1 and 2 times the normal, we see 11 percent of Ketek treated patients achieving this level of elevation and nine percent of comparator treated patients achieving this level of elevation and then a few events in both arms at higher levels.

Now, ALT changes occurring at the post-therapy visit, day 17 to 21, and again, the same ladder as we've been looking at for ALT and if we look at the level of one times to less or equal to two times normal, we see 12 percent of the Ketek treated patients achieving that level and nine percent of comparator treated patients achieving that level.

And now within your packet there's a loose slide that should replace the one that's currently in there for slide 12. This table looks at combined laboratory abnormalities of ALT, AST and T. bilirubin at the level of greater than the upper limit of normal and less than two times normal and if we look at the right most column, we have the category of lab analytes where we have combined AST, ALT and T. bilirubin and then either ALT and T. bili or AST and T. bili and we have the number of patients achieving that level of elevation for the Ketek treated patients and for the comparator treated patients.

I should note the Ketek treated patients includes patients both from the comparative and the non-comparative studies. And we see we have five events for all three analytes, five for ALT and T. bili, one for AST and T. bili and from the comparator studies, the comparator treated patients we don't have

any events there.

And then with regards to combined abnormalities, the late Dr. Hy Zimmerman, in his book, "Hepatoxicity", stated that drug induced hepatocellular injury with overt jaundice is associated with a morality of at least 10 percent. This phrase has come to be known as Hy's Law within the agency and as a surrogate for Hy's Law within NDA data bases, we often times look at AST or ALT greater than three times the upper limit of normal combined with a T. bilirubin elevation of greater than 1.5 times the upper limit of normal.

And in the Ketek treated arm and the comparator treated arms, there were no patients that met this criteria strictly. Now, there is -- there are some patients in the Ketek arm I'd like to comment on. The first is the patient who has an ALT elevation of 19 times the upper limits of normal and a T. bilirubin of 1.55 times the upper limit of normal. Now, the is patient also had an ALT at 81 at baseline, so he did have a slight elevation and this is the same patient for whom Dr. Goodman will be describing the pathology on the liver biopsy shortly.

There were two other patients who didn't quite achieve the level of elevation of three times

and 1.5 times the upper limit of normal but were close. One of these two patients had a mild increase in alkaline phosphatase. And now what I'd like to do is just describe the cases of serious adverse events that occurred during the NDA data base. And one of the reasons that I'm spending some time going over these cases and describing them in some detail is that within the NDA studies, you know, the safety data bases really are not powered to find infrequent occurring events and I think going through these cases may provide us some insights.

The first serious adverse event I'll describe is a comparator treated patient. This patient was a 61-year old male with community-acquired pneumonia a history of congestive heart failure and alcoholism who was maintained on Digoxin. He was treated with Clarithromycin, 500 milligrams po BID for 10 days. He was noted to be jaundiced on day 17 and as part of his evaluation had a CT scan and an ultra-sound examination that showed changes consistent with a disseminated neoplasm thought to be of either hepatic or renal origin.

And I've provided some of his abnormal lab values below. His peak T. bili was approximately five times the upper limit of normal and his alkaline

phosphatase was also approximately five times the upper limit of normal. His AST and ALT were normal.

And then this is the first serious hepatic adverse event from the Ketek studies, a 76 year old female with community-acquired pneumonia, a history of hypocholestral anemia and hypercholesterolemia who's maintained on Pravastatin and Allopurinol chronically. She received treatment with Ketek, 800 milligrams po daily on days 1 through 6. And then in this table in the right most column we have the laboratory analytes. Next to those, their corresponding normal ranges. And we note that at the time that this patient was enrolled in the study, she had a slightly elevated AST. She receives therapy on day 5. Her AST and ALT are elevated at AST of 295, ALT of 418 with a T. bili and alkaline phosphatase that are just slightly elevated.

On day 6 she stops her Ketek therapy. On day 7 we see her AST and ALT returning towards normal and continuing to do so at her subsequent visit.

The second serious hepatic adverse event from the Phase III studies involved a 19-year old male with tonsillar pharyngitis who had a positive culture for Group A Beta hemolytic strep and no significant past medical history. The patient was treated with

Ketek, 800 milligrams daily from days 1 through 5 and then on the evening of day 12, there's a history of heavy alcohol consumption. And the similar design to the table on the last slide, on the right most column the analytes and we see he had normal liver function tests when he began the study. We have the completion of Ketek therapy at day 5, the history of alcohol intake at day 12 and then on day 13 we see the bumps in AST and ALT with the increase in AST being greater than that of what was experienced with ALT and then subsequent resolution over the next few visits.

And this is the case the Dr. Goodman will be describing the pathology on shortly. This is the case of a 53-year old male from Finland with a -- who was admitted to one of the CAP studies who had a history of asthma and diabetes mellitus and he was maintained on inhaled Salbutamol, Fluticasone, Attrovent, Nasonex and oral calcium. There's also a history of Acetaminophen intake that began on day 13 and it's described in the case report forms as the intake of six times 500 milligram tablets of Tylenol over one week. The patient was treated with Ketek 800 milligrams daily, days 1 through 10 and then on day 14 he developed an illness that included fever, vomiting, diarrhea. This was an illness that was similar to an

illness that other members of his family were experiencing at the same time. The difference in the patient's illness was that his fever persisted.

Now, I'd like to go through his laboratory studies, again, a similar table. We've added the Eosinophils here at the bottom of the table and we have normal ranges. The normal range for Eosinophils, we don't have a laboratory specific normal range, so we're using the typical normal range of less than 500 cells per micro-liter. And on day 1 we note a mild increase in ALT of 81 and the Eosinophil count of 774. The patient receives Ketek day 1 through 10 and then returns on day 21 for a follow-up evaluation after he's had this febrile illness with persisting fever. He is noted to have an ALT of 354. We see further increase in his Eosinophil count and then on day 24 his ALT achieves a maximum for the course of this particular episode of hepatitis of 1529 and I've also included data from day 35 here when his ALT is down to 518 and this is the maximum Eosinophil count attained during this episode.

As part of the patient's evaluation for his episode of Hepatitis, the patient had serologies for Hepatitis A, B and C that were negative. He went on to have a liver biopsy on Day 29, and Dr. Goodman

will describe the pathology there shortly. And then the patient's ALT had normalized by three months.

Now the patient went on and had a second event of Hepatitis, and this was noted approximately eight months after the first event at a routine follow, when the patient had an ALT value of 1331. As part of this evaluation, the patient had Anti-Smooth Muscle Antibodies drawn there were positive one to one thousand. The patient was also noted to have an elevated IGG and IGA. With the second episode, Eosinophilia was not present, and a second liver biopsy was also attained for the second episode.

And now I'd like to turn the podium over to Dr. Zachary Goodman, who will describe the findings from the liver biopsies from this patient.

DR. GOODMAN: Well, you'll see that on the schedule I'm listed as giving a lecture on drug-induced liver disease, but I'm really going to focus on the liver biopsy and drug-induced liver disease. And I should say at the start that liver biopsy is not usually done in somebody in whom you strongly suspect drug-induced liver disease. If a patient is on a drug, develops liver test abnormalities, and you stop the drug and the test abnormalities go away, then a liver biopsy is not indicated.

The times that liver biopsies are done is when there's a confusing clinical situation, when it might be one thing or another; or when the diagnosis of drug-induced liver disease is not entertained. And when we're talking about drug-induced liver disease, we're not talking about usually intrinsic toxicity, but an idiosyncratic reaction; and so what do you see in the liver biopsy in somebody who has an idiosyncratic drug-induced injury? Well, it could be anything.

One of the principles and one of the points to be made is that drugs can mimic just about anything that can happen in the liver, anything that can happen in any naturally occurring liver disease can happen in drug-induced liver disease; so when you get a liver biopsy from somebody in whom drug-induced injury has occurred, it can show just about anything. You can have an acute injury, or you can have a chronic injury. And the acute injury can take the form of hepatocellular injury, a cholestatic injury, a mixture of the two, or some sort of vascular injury. And a chronic injury can be a chronic hepatocellular injury; that is it can be a chronic hepatitis, you can have chronic cholestasis, you have granulomas disease, fibrosis or cirrhosis, a vascular injury, or tumors.

And so in other words, the drugs can mimic absolutely anything.

So just to give some examples from the area of antibiotics; some examples, tetracyclines typically cause microvesicular fat in a dose related more intrinsic toxic injury, but sometimes tetracyclines can cause chronic cholestasis, although very rarely; and tetracyclines can cause chronic hepatitis, particularly with minocycline.

And one of the principles of recognizing drug-induced injury is that the same drugs tend to do the same thing over again; that there is a certain range of patterns that are seen with each particular agent in which drug induced injury is recognized.

For amoxicillin and calvulonic acid, typically that causes cholestatic injury; but there can also be an element of cholangitis, or it can be combined with hepatocellular injury, or sometimes granulomas. Nitrofurantoin has been around for a long time, long enough to establish a relative incidence of injury; and it's estimated that about one in every 3,000 individuals who takes nitrofurantoin will develop liver injury. And the injury can take the form of various forms of acute hepatitis, of acute hepatocellular injury about 30 percent of the time,

chronic injury about half of the time, cholestatic injury in about 10 percent and other 10 percent is miscellaneous things.

So then the question arises when we've got a liver biopsy from somebody, when should we suspect that a drug might have been the cause; and one answer is always we always suspect it since drugs can mimic anything that can happen in the liver. If there's not an obvious other cause, then we always inquire about what drugs the patient was taking. But we're especially suspicious of a drug-induced injury when there's some sort of atypical pattern; that is, something that's not usually seen in the usual range of liver diseases, so such things as a combined hepatocellular and cholestatic injury, that is cholestatic hepatitis that can happen in viral hepatitis. But in a liver biopsy performed in a hospital in the developed world when you see a cholestatic hepatitis, it's much more likely a drug than viral hepatitis.

Granulomas hepatitis; both granulomas and hepatocellular injury, sometimes that happens in zarquoidosis, but it's more likely to be a drug. And especially if we see a hepatitis that has a lot of eosinophils with it, not absolutely 100 percent of the

time, but usually it turns out to be a drug. And when you have a really severe injury, and particularly one in which there's zonal necrosis, that's also most often due to a drug.

So let - excuse me - let me show a few examples. Could we dim the lights just a little bit? Does anybody know where the light switch -- for those of you who have been out of medical school for a while, I'll remind you of what normal liver histology looks like.

You'll recall that a liver has portal areas and it has central veins, and the portal areas have portal vein branches, hepatic artery branches and bile ducts, and the blood comes into the liver at the tissue level through the vessels of the portal triades, and percolates through the sinusoids of the liver where the business of the liver takes place by the hepatocytes, and the blood leaves the liver through the central veins.

Now some important points are that the area around the central vein has the blood with the least oxygen and the least nutrients, so it's most susceptible to several types of injury. It's most susceptible to ischemic injury.

The area around the central vein is also